In the Specification

Kindly insert the following paragraph before paragraph [0001], as published:

Related Application

This application is a 371 of PCT/EP04/51755 with a filing date of August 9, 2004, which claims priority of EP Application No. 03447210.0 with a filing date of August 14, 2003.

Kindly replace paragraph [0001] with the following:

TECHNICAL FIELD ~~OF THE INVENTION~~

[0001] Delivery of a therapeutic agent locally, in particular from an intraluminal prosthesis such as a coronary stent, directly from the surface of the prosthesis or from pores, micropores, perforations or pits in the prosthesis body, directly bounded on the prosthesis or mixed or bound to a polymer coating applied on the prosthesis, or mixed or bound to a glue applied to the prosthesis, to modulate the healing response after vascular injury, to improve endothelial cell regrowth, and to inhibit inflammation induced by the injury caused by the implantation of the intraluminal prosthesis and inhibiting tissue proliferation and thereby preventing stenosis of the prosthesis.

Kindly replace paragraph [0002]as published with the following:

BACKGROUND ~~OF THE INVENTION~~

[0002] Re-narrowing (restenosis) of an atherosclerotic coronary artery after percutaneous transluminal coronary angioplasty (PTCA) occurs in 10-50% of patients undergoing this procedure and subsequently requires either further angioplasty or coronary artery bypass graft. While the exact hormonal and cellular processes promoting restenosis are still being determined, the present understanding is that the process of PTCA, besides opening the atherosclerotically obstructed artery, also injures resident coronary arterial smooth muscle cells (SMC). In response

to this injury, adhering platelets, infiltrating macrophages, leukocytes, or the smooth muscle cells (SMC) themselves release cell derived growth factors with subsequent proliferation and migration of medial SMC through the internal elastic lamina to the area of the vessel intima. Further proliferation and hyperplasia of intimal SMC and, most significantly, production of large amounts of extracellular matrix over a period of 3-6 months results in the filling in and narrowing of the vascular space sufficient to significantly obstruct coronary blood flow.

Kindly replace paragraph [0015] as published with the following:

~~Novel Features and Applications to Stent Technology~~

[0015] Currently, attempts to improve the clinical performance of endoluminal prosthesis such as coronary stents have involved some variation of either searching for a more biocompatible metal alloy, ~~optimising~~ optimizing the stent surface, applying a coating to the metal, attaching a covering or membrane, or embedding material on the surface via ion bombardment. A stent designed to include reservoirs that can be filled up with therapeutic agents, influencing the restenosis process has also been proposed.

Kindly replace paragraph [0016] as published with the following:

~~Local Drug Delivery from an Endoluminal Prosthesis such as a Stent to Inhibit Restenosis~~

[0016] In ~~this~~ that application, a therapeutic agent is delivered to the site of arterial injury. The conventional approach has been to incorporate the therapeutic agent into a polymer material which is then coated on the stent. The ideal coating material must be able to adhere strongly to the metal stent both before and after expansion, be capable of retaining the drug at a sufficient load level to obtain the required dose, be able to release the drug in a controlled way over a period of several weeks, and be as thin as possible so as to minimize the increase in profile. In addition, the coating material should not contribute to any adverse response by the body and

should be perfectly biocompatible (i.e., should be non-thrombogenic, non-inflammatory, etc.). To date, the ideal coating material has not been developed for this application.

Kindly replace paragraph [0018] as published with the following:

[0018] ~~An other~~ Another alternative is to use a drug impregnated biocompatible glue, in particular a biocompatible oil/solvent emulsion. Also with ~~this~~ that method the drug release is quite fast, but combination with a barrier coating could improve the release characteristics.

Kindly replace paragraph [0020] as published with the following:

~~Pharmacologic Attempts to Prevent Restenosis~~

[0020] Pharmacological attempts to prevent restenosis by pharmacologic means have thus far been unsuccessful and all involve systemic administration of the trial agents. Neither aspirin-dipyridamole, ticlopidine, acute heparin administration, chronic warfarin (6 months) nor methylprednisolone have been effective in preventing restenosis although platelet inhibitors have been effective in preventing acute reocclusion after angioplasty. The calcium antagonists have also been unsuccessful in preventing restenosis, although they are still under study. Other agents currently under study include thromboxane inhibitors, prostacyclin mimetics, platelet membrane receptor blockers, thrombin inhibitors and angiotensin converting enzyme inhibitors. These agents must be given systemically, however, and attainment of a therapeutically effective dose may not be possible; antiproliferative (or anti-restenosis) concentrations may exceed the known toxic concentrations of these agents so that levels sufficient to produce smooth muscle inhibition may not be reached (Lang et al., 42 Ann. Rev. Med., 127-132 (1991); Popma et al., 84 Circulation, 1426-1436 (1991)).

Kindly replace paragraph [0026] as published with the following:

SUMMARY ~~OF THE INVENTION~~

[0026] ~~Melatonin (N-acetyl-5-methoxytryptamine) or a Melatonin Derived Drug Coated on an Endoluminal Prosthesis to Modulate the Healing Response after Vascular Injury by Decreasing Vascular Injury and Inflammation Caused by the Implantation of the Prosthesis and Resulting in a Decreased Neointimal Hyperplasia~~. A stent implantable at least partially in a blood vessel in contact with a wall of the blood vessel and comprising at least one releasable therapeutic agent coated directly on a surface of the stent which is free from a biocompatible coating, wherein the releasable therapeutic agent comprises melatonin (N-acetyl-5-methoxytryptamine) and/or a drug derived from melatonin and having analogous effects on the healing response of the vessel wall, the therapeutic agent being present in an amount effective to modify the healing response of the vessel wall after tissue injury caused by the implantation of the stent by inhibiting inflammation, cell proliferation and cell in growth into the stent.

Kindly replace paragraph [0027] as published with the following:

DETAILED DESCRIPTION

[0027] ~~In accordance with the present invention,~~ We use ~~is made of~~ Melatonin to coat the endoluminal prosthesis. Instead of and/or in addition to melatonin, use could also be made of a drug derived from melatonin, i.e. a drug which has a similar chemical structure, and which has analogous effects, in particular substantially the same effects, on the healing response of the blood vessel wall. In vitro evidence demonstrates that melatonin has a mode of action which is different from that of rapamycin. Melatonin has been shown to possess anti-inflammatory effects, among a number of other actions. Melatonin reduces tissue destruction during inflammatory reactions by a number of means. Melatonin, by virtue of its ability to directly scavenge toxic free radicals, reduces macromolecular damage in all organs. The free radicals and reactive oxygen and nitrogen species known to be scavaged by melatonin include highly toxic

hydroxyl radicals (--OH), peroxynitrite anion (ONOO--), and hypochlorous acid (HOCL), among others. These agents all contribute to the inflammatory response and associated tissue destruction. Additionally, melatonin has other means to lower the damage resulting from inflammation. Melatonin prevents the translocation of nuclear factor-kappa B (NF-kappaB) to the nucleus and its binding to DNA, thereby reducing the upregulation of a variety of proinflammatory cytokines, for example, interleukins and tumor necrosis factor alpha. Finally, there is indirect evidence that melatonin inhibits the production of adhesion molecules that promote the sticking of leukocytes to endothelial cells. By this means melatonin attenuates transendothelial cell migration and edema, which contribute to tissue damage.

Kindly replace paragraph [0029] as published with the following:

[0029] So far local delivery of melatonin was used in coated veterinary implants for regulation of seasonal breeding and other physiological responses. WO 98/30255 ~~mentiones~~ <u>mentions</u> ~~localised~~ <u>localized</u> intravascular delivery of probucol, and of a series of other antioxidant substances including melatonin, in an amount sufficient to inhibit restenosis in recanalized blood vessels. Most commonly, use is made of a specially designed local drug delivery catheter but, in some cases, it may be advantageous according to WO 98/30255 to employ implanted devices, such as implanted stents capable of delivering the antioxidant substance for prolonged periods of time. Disadvantage of the use of a local drug delivery balloon is that the drug can only be released during a limited time period (up to 5 minutes) and that the efficacy of effective local drug delivery to the vascular wall is very low (<1%-5%) and very variable. So far no beneficial effect of using localized intravascular delivery of antioxidant substances like described in WO 98/30255 for the inhibition of restenosis in recanalized blood vessels, using a local drug delivery balloon nor a drug coated stent has been shown, especially even not in WO 98/30255 itself. For

melatonin, no proof is given in WO 98/30255 that melatonin may be effective in inhibiting restenosis. Instead, a reference is made for the antioxidant substances, different from probucol, to U.S. Pat. No. 5,326,757; WO 95/26193 and CA 2 106 695 disclosing however specific combinations of selected antioxidant substances (no melatonin) or a combination of antioxidant substances (Vitamin C) with hyaluronic acid to enhance the effect of this hyaluronic acid in preventing narrowing of tubular walls. For probucol, which is according to WO 98/30255 the preferred antioxidant, reference is on the contrary made to publications demonstrating the effectiveness of probucol for inhibiting restenosis. Consequently, for a skilled person it is clear that in the some cases wherein it may be advantageous to use an implanted stent instead of a drug delivery catheter, the antioxidant substance should be the preferred probutol since it is clear that the amount of the antioxidant substance which can be delivered with an implanted stent is much smaller than the amount that can be delivered with a catheter and that much larger amounts of the other antioxidant substances will be required to inhibit restenosis than of the more effective probucol. WO 98/30255 thus does not teach the combination of an implanted stent coated with melatonin so that this combination is novel with respect to WO 98/30255. Based on the teachings of WO 98/30255 a skilled person could try to deliver probucol by means of an implanted stent but, if that does not give the desired results on inhibiting restenosis, it is not obvious for him to try also the other antioxidant substances which were for the skilled person apparently less effective in inhibiting restenosis than probucol.

Kindly replace paragraph [0030] as published with the following:

[0030] ~~The present invention is~~ <u>Our stents and methods are</u> now based on the unexpected potent beneficial effect of local, stent mediated melatonin delivery on the vascular injury and inflammation, most probably due to the potent neutralizing effect of toxic free radicals, released

during injury induced inflammation, by melatonin, combined with its direct anti-inflammatory effects, resulting in an improved healing, less smooth muscle cell stimulation and proliferation and less cellular ingrowth and narrowing of an endoluminal implant, endovascular prosthesis, shunt or catheter.

Kindly replace paragraph [0031] as published with the following:

Experimental with Melatonin (N-acetyl-5-methoxytryptamine) Coated Coronary Stents:

[0031] To get rid of the polymer, which remains always a concern when coating a drug on an endoluminal prosthesis, since several polymers have shown to be non biocompatible and to induce an inflammatory response leading to SMC proliferation and restenosis, ~~the present inventor~~ we tried to coat melatonin directly to the surface of the endoluminal prosthesis. As endoluminal prosthesis use was made of a commercially available 316L stainless steel coronary stent (V-Flex Plus, 16 mm/3.0 mm, William Cook Europe) and the stent was dipped in a 20 mg/ml ethanol solution for 30 seconds. After removal the stent was air-dried using a warm laminar flow to evaporate the ethanol. Using this method a total melatonin load on the stent of 20 μg could be achieved. Implantation of these stents in a porcine coronary model with follow-up after 5 days revealed perfect biocompatibility of the system, without inducing any inflammation surrounding the struts of the stents on histological examination. After 4 weeks a 26% decrease in neointimal hyperplasia was surprisingly found compared to a bare stent. Similar experiments, using probucol, did not result in a significant effect on inflammatory response and neointimal hyperplasia. Notwithstanding the low total dose of melatonin (20 μg), significant efficacy with this system could be demonstrated. This could be explained by the 1) the potent free radical scavenging effect of melatonin, 2) the potent anti-inflammatory effect of melatonin, 3) maybe a

direct effect on SMC proliferation, 4) the non toxic effect of melatonin on other mediators of the healing response.